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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/588,554	08/07/2006	Joel M. Van Gelder	VAN GELDER1A	8291

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EXAMINER	
SZNAIDMAN, MARCOS L	

ART UNIT	PAPER NUMBER
4173	

MAIL DATE	DELIVERY MODE
12/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,554	VAN GELDER ET AL.	
	Examiner	Art Unit	
	Marcos L. Sznaidman	4173	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-8,13-20,22-67 and 136-140* is/are pending in the application.

4a) Of the above claim(s) *2-4,6-8,13-15,19,20,22-54,56,59-67,136,137 and 140* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,16-18,55,57,58,and 138-139* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group IV (claims 1, 16-18, 54-67, and 137-140) in the reply filed on November 1, 2007 is acknowledged.

Applicant's election without traverse of compound 106 as the compound species, and melanoma as the disease species in the reply filed on November 1, 2007 is also acknowledged.

Status of Claims

Claims 1-4, 6-8, 13-20, 22-67 and 136-140 are currently pending and are the subject of this office action.

Claims 2-4, 6-8, 13-15, 19-20, 22-54, 56, 59-67, 136-137 and 140 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions/species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 1, 2007.

Claims 1, 16-18, 55, 57-58, and 138-139 are currently under examination.

Priority

This application is a 371 of PCT/IL05/00149 filed on 02/06/2005, which claims benefit of Provisional Application No. 60/541,904 filed on 02/06/2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 16-18, 55, 57-58, and 138-139 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996). As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1- the quantity of experimentation necessary,

2- the amount of direction or guidance provided,

3- the presence or absence of working examples,

4- the nature of the invention,

5- the state of the prior art,

6- the relative skill of those in the art,

7- the predictability of the art, and

8- the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to a method for treatment of a disease or disorder (melanoma is the species elected) caused by or associated with heparanase catalytic activity, said method comprising administering to a patient in need an effective amount of a heparanase inhibitor of the general formula **Id** (see claim 16, compound 106 is the species elected).

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

The factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies with the degree of unpredictability of the factors involved", and physiological activity is considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved); *Nationwide Chemical Corporation, et. al. v. Wright, et. al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances); *Ex parte Sudilovsky* 21 USPQ2d 1702 (Applicant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable); *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian vaccine was uncertain).

As illustrative of the state of the art for treating cancer in general, the examiner cites Gura et. al. (Science, 1997, 278:1041-1042), and Johnson et. al. (British Journal of Cancer, 2001, 84:1424-1431. Gura et. al., cited for evidentiary purposes, teaches that researches face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and further teach that since formal screening began in 1955, many thousand of drugs have shown activity in either cell or animal models, but only 39 have actually been shown useful for chemotherapy (see page 1041, first and second paragraph). Also, with regard to unpredictability,

Johnson et al., also cited for evidentiary purposes, teach that the in vivo activity of 39 different agents in a particular histology in a tumor model did not correlate to activity in the same human cancer (see Results on page 1426). *In re Fisher*, 427 F.2d 833,166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Further, the mode of action of anticancer agents is often unknown or very unpredictable and administration of such agents is often accompanied by undesirable side effects.

Regarding more specifically to the treatment of different types of cancer with inhibitors of heparanase the examiner cites: Ishida et. al. (The Journal of Antibiotics, 2004, 57:136-142), Courtney et. al. (Bioorganic and Medicinal Letters, 2004, 14:3269-3273), and McKenzie (British Journal of Pharmacology, 2007, 151:1-14). Ishida et. al. teach that most heparanase inhibitors reported by now (February 2004) are derivatives of sulfated oligosaccharides similar to the substrate Heparan Sulfate, and not low molecular weight compounds (see page 136, column 2, second paragraph). Courtney et. al. also teach that even though Heparanase offers an attractive drug target, progress in this area has been limited by the current available repertoire of inhibitors. The most advanced inhibitor is PI-88 (a highly sulfonated mannan oligosaccharide), which is currently in Phase II clinical trials (and so far the only known heparanse inhibitor in clinical trials, see page 3269 first paragraph). So there are still no small molecule inhibitors of heparanase in human trials for the treatment of any type of cancer. In a recent review (2007), McKenzie shows that there are very few small molecules available as heparanase inhibitors, and only in one case they show animal data in a

B16-Bl6 melanoma tail vein model (see page 7 under "Small molecule inhibitors: Imclone Systems Incorporated). They also mention, regarding another group of small molecule heparanase inhibitors, that unfortunately there is no published data on the efficacy of any of the small molecule inhibitors in animal studies, hence it remains to be seen whether these compounds will actually have efficacy *in vivo* (see page 7, first paragraph).

These articles plainly demonstrate that the art of developing and testing anticancer drugs, particularly for use in humans, is extremely unpredictable, particularly in the case of a single compound or genus of compounds being used to treat any and all cancers or different type of diseases. There are also no examples of small molecule heparanase inhibitors in the prior art for any of the following cases: 1- correlation of the in vitro inhibition and efficacy in humans, 2- there are very few examples correlating *in vitro* inhibition and efficacy in animals, and 3- there are no examples of correlation between efficacy in animal models and efficacy in humans.

2. The breadth of the claims

Even though the current examination is restricted to compound 106 and melanoma as the type of cancer to be treated, applicant should be aware that the claims vary in breadth; some (such as claims 1, 16, 17) vary broadly, reciting the treatment of broad genus of diseases with a broad genus of compounds. Others, such as claim 18 are narrower, reciting specific species of the claimed genus of compounds, but still claiming a broad genus of diseases.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification only provides *in vitro* heparanse inhibition data for compounds 1-107. There is no animal data to corroborate that these compounds will have efficacy in animals, even less in humans. The specification provides no direction or guidance for determining the particular administration regimens (e.g., dosages, timing, administration routes, etc) necessary to treat melanoma with compound 106. The directions concerning treating cancer (melanoma) are found in the specification at pages 41-44 and 64-68, which merely states Applicants' intention to do so by providing *in vitro*, *ex vivo* and *in vivo* assays, but no compounds were actually tested in those assays, except for the *in vitro* heparanase inhibition mentioned at the beginning of this paragraph.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept that instantly claimed compound 106 could be predictably used as treatment for melanoma. Since there is no precedent in the literature for the treatment of melanoma with any of the claimed compounds or similar compounds, how is the skilled physician supposed to know how to dose this compound in order to treat melanoma? Determining if the claimed compound 106 (or any of the non-elected compounds), would treat melanoma (or any particular cancerous disease) would require

formulation into a dosage form, and subjecting into clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by Applicants.

Accordingly, the inventions of claims 1, 16-18, 55, 57-58, and 138-139 do not comply with the enablement requirement of 35 U.S.C 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation with no assurance of success.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcos L. Sznaidman whose telephone number is 571 270-3498. The examiner can normally be reached on Monday through Friday 9 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on 571 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MLS
November 28, 2007

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614